Concepts of Palliative Care

Oncology Fundamentals Day
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September 28, 2019

Disclosures

I have no conflicts of interests to declare

Learning Objectives

1.) Review the history and define the philosophy of palliative care

2.) Recognize causes of dyspnea and identify potential treatment options

3.) Identify causes for cancer related fatigue and compare the effectiveness of pharmacological and non-pharmacological management

4.) Define anorexia-cachexia and analyze the literature surrounding pharmacological treatment

5.) Differentiate the subtypes of delirium and examine treatment options

6.) Discuss the principle of palliative sedation in palliative care

History and Principles of Palliative Care

Question Time

What is the prognosis of a “palliative” patient?

A. Hours to days
B. Days to weeks
C. Weeks to months
D. Years
E. All of the above

Answer

What is the prognosis of a “palliative” patient?

A. Hours to days
B. Days to weeks
C. Weeks to months
D. Years
E. All of the above

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Definition

- Palliative care:
  - Relieve symptoms of someone with an incurable disease
  - Improve quality of life
  - Does not hasten death
  - Helps improve quality of life of family members
  - Can be used early in the course of illness in conjunction with life prolonging therapy

Website: https://www.who.int/cancer/palliative/definition/en/

History of Palliative Care

- Origins from Dr. Cicely Saunders
  - Founded the first hospice
- Belief that pain was “total pain”
- Individuals dying should be treated as individuals with dignity
- Introduced effective pain management
- “It appears that many patients feel deserted by their doctors at the end”

BMJ 2005;331:238

Temel Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer

Jennifer S. Temel, M.D., Joseph A. Greer, Ph.D., Alona Muzikansky, M.A., Emily R. Gallagher, R.N., Sonal Admane, M.B., B.S., M.P.H., Vicki A. Jackson, M.D., M.P.H., Constance M. Dahlin, A.P.N., Craig D. Blinderman, M.D., Juliet Jacobsen, M.D., William F. Pirl, M.D., M.P.H., J. Andrew Billings, M.D., and Thomas J. Lynch, M.D.

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Effects of Early Integrated Palliative Care in Patients With Lung and GI Cancer: A Randomized Clinical Trial

Jennifer S. Temel, Joseph A. Greer, Areej El-Jawahri, William F. Pirl, Elyse R. Park, Vicki A. Jackson, Anthony L. Back, Mihir Kamdar, Juliet Jacobsen, Eva H. Chittenden, Simone P. Rinaldi, Emily R. Gallagher, Justin R. Eusebio, Zhigang Li, Alona Muzikansky, and David P. Ryan

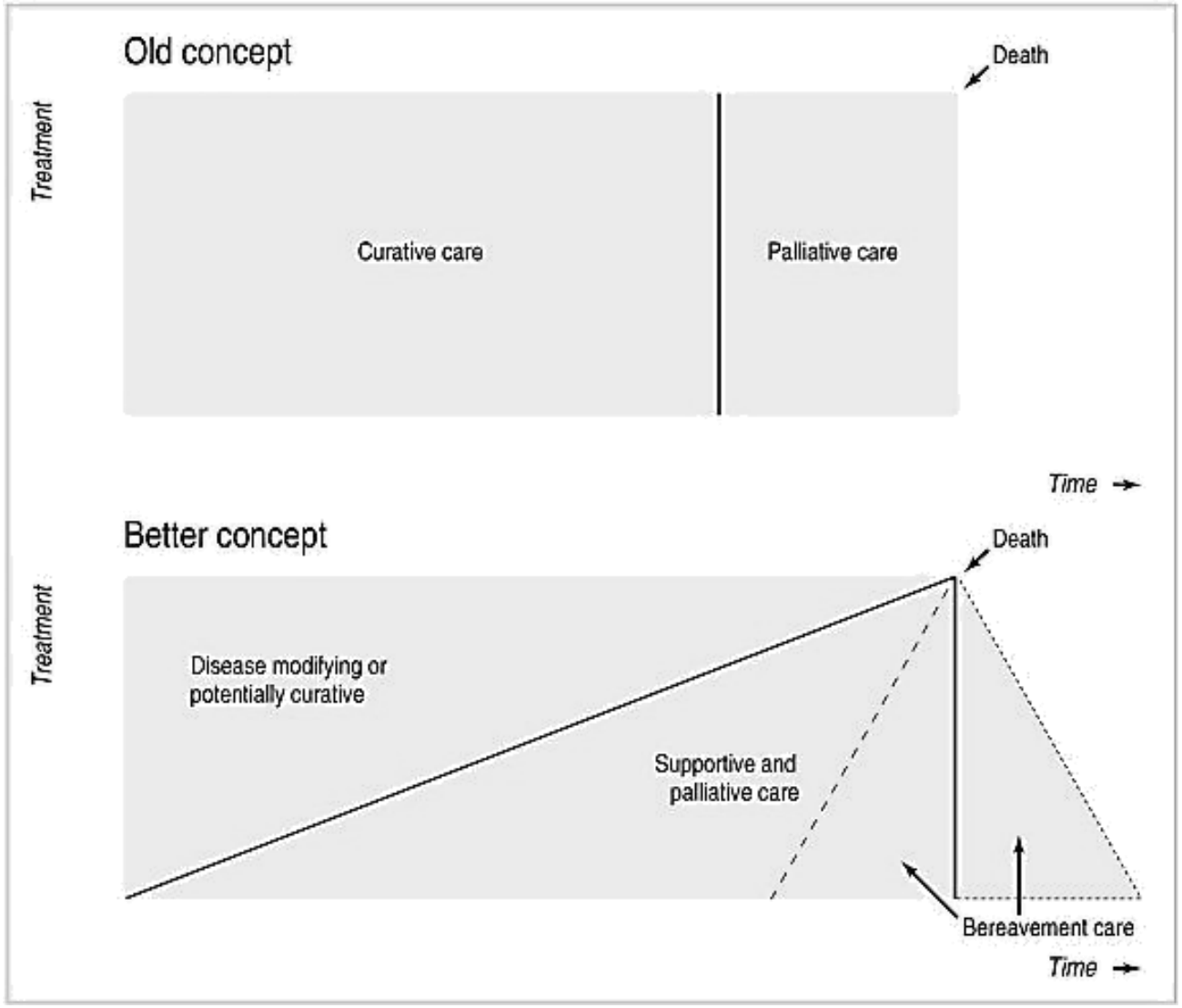
N Engl J Med. 2010 Aug 19;363(8):733-42
J Clin Oncol. 2017 Mar 10;35(8):834-841

Temel Study

- 2010 NEJM study
  - Metastatic non-small cell lung cancer
  - Early palliation demonstrated improved depressive symptoms, quality of life, and median survival
- 2017 JCO study
  - Incurable lung cancer or non colorectal GI cancer
  - Intervention group – meeting with palliative care doctor once per month vs. standard care at the end of life
  - Improvement in quality of life and depressive symptoms at week 24

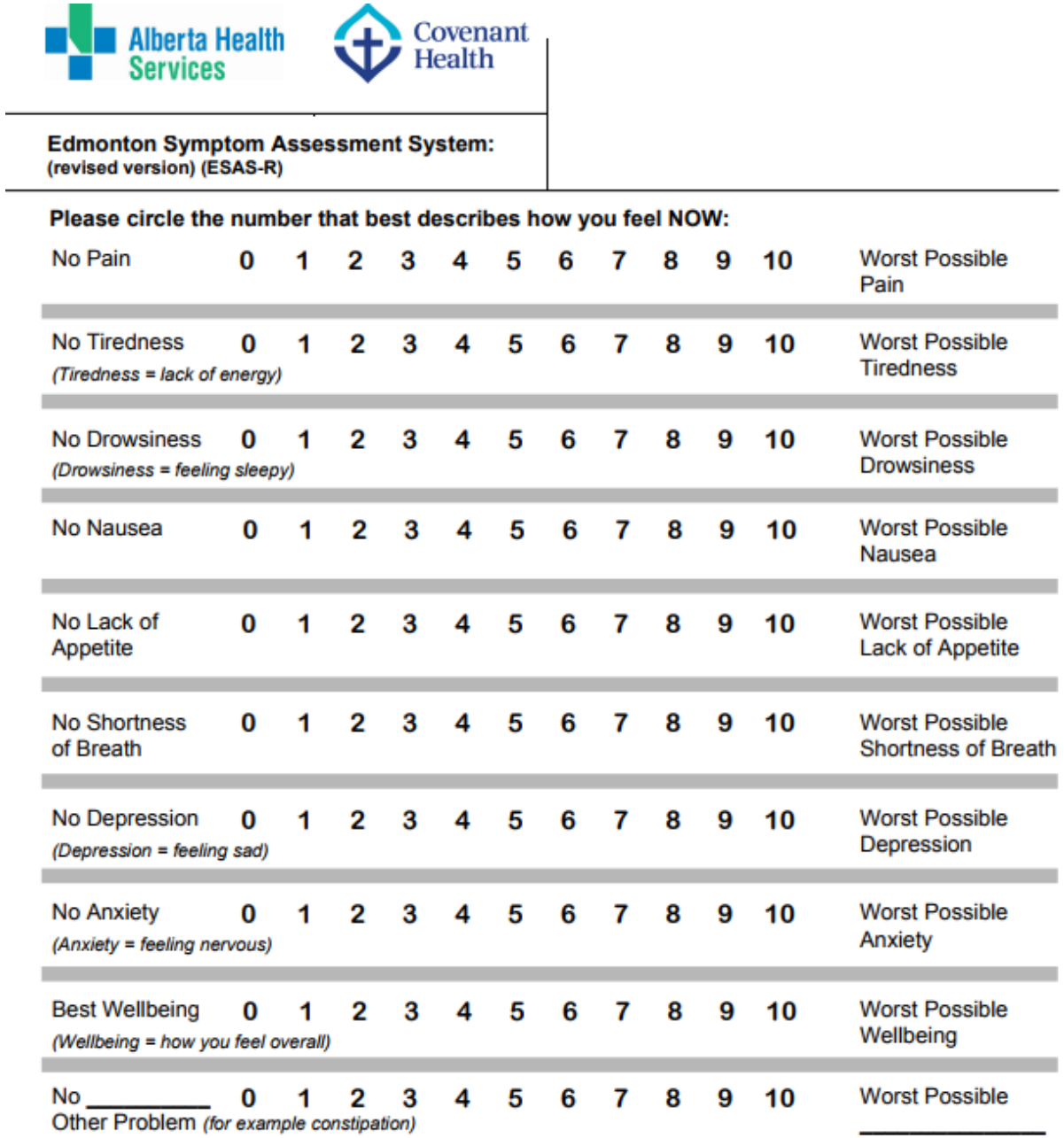
N Engl J Med. 2010 Aug 19;363(8):733-42
J Clin Oncol. 2017 Mar 10;35(8):834-841

Palliative Trajectory



BMJ. 2005 Apr 30; 330(7498): 1007–1011

Assessment Tools



Alberta Health Services

Covenant Health

Edmonton Symptom Assessment System:
(revised version) (ESAS-R)

Please circle the number that best describes how you feel NOW:

No Pain	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Pain
No Tiredness *(Tiredness = lack of energy)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Tiredness
No Drowsiness *(Drowsiness = feeling sleepy)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Drowsiness
No Nausea	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Nausea
No Lack of Appetite	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Lack of Appetite
No Shortness of Breath	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Shortness of Breath
No Depression *(Depression = feeling sad)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Depression
No Anxiety *(Anxiety = feeling nervous)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Anxiety
Best Wellbeing *(Wellbeing = how you feel overall)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Wellbeing
No _____ Other Problem *(for example constipation)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible _____

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Case Presentation

B.B is a 64 year old female with breast cancer metastatic to the bone

- Diagnosed in 2014 – docetaxel and cyclophosphamide x 4 cycles then adjuvant tamoxifen treatment
- Progression in 2018 – metastatic to the spine and ribs
- No known drug allergies

Case Presentation

- Current medications
  - Hydromorphone 2 mg PO q4h around the clock
  - Hydromorphone 1 mg PO q1h PRN
  - PEG 3350 17 g PO daily
  - Metoclopramide 10 mg PO four times daily PRN
  - Recently discontinued ramipril, hydrochlorothiazide, and rosuvastatin
- Pain rated at 3/10 post palliative radiation
- B.B comes in today asking “I have been having difficulties with shortness of breath, would an inhaler help?”

Question Time

Which of the following is true?

A. Dyspnea often accompanies a reduction in oxygen saturation
B. Opioids are effective in the management of dyspnea
C. Inhalers, such as salbutamol, are first line agents in management of dyspnea associated with cancer
D. Dyspnea is an objective symptom
E. Dyspnea is most prevalent in patients with pain and bone metastases

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Answer

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Dyspnea

Dyspnea

- Subjective experience of breathing discomfort
  - Uncomfortable awareness of breathing
  - Most prevalent in lung cancer patients
  - Oxygen saturation can remain normal
    - Focus on the patient, not the number
  - “Suffocating” “Choking” “Cannot breathe”

Ann Oncol. 2015 Sep;26 Suppl 5:v169-73

Causes

- Multifactorial with complex pathophysiology
  - Neurobiological
    - Mismatch or imbalance of afferent impulses from sensory receptors and the demand to breathe in comparison with the muscles and ability to breathe
    - Air hunger with autonomic response due to carbon dioxide concentrations
  - Psychological
    - Anxiety
    - Depression

Expert Rev Respir Med. 2013 Apr;7(2):123-34

Causes

- Rule treat underlying comorbidities
  - COPD
  - Lung primary or lung metastases
  - Tumor obstructing airway
  - Pulmonary embolism
  - Pleural effusions
  - Pulmonary toxicity from treatment
  - Ascites/hepatomegaly elevating diaphragm
  - Congestive heart failure
  - Anxiety
  - Muscle weakness from deconditioning and advanced cancer
  - Infection
  - Mediastinal lymphadenopathy

Pharmacological Management

- Opioids
  - Decrease respiratory responsiveness in the brainstem respiratory centers associated with hypoxia and hypercapnia
  - Modulate central processing of dyspnea, similar to pain relief
  - Opioid receptor modulation in the bronchioles and alveolar walls
- Does NOT hasten death
- Start at a low dosage and titrate
- Consider oral dosing or sublingual/buccal
  - If needed can use subcutaneous or intravenous
- Nebulized opioids not effective

Expert Rev Respir Med. 2013 Apr;7(2):123-34

Pharmacological Management

- Dosing should be titrated based on case by case basis
- As needed dosages for incidental dyspnea
- Start as PO/SL/Buccal but if needed can use SC/IV routes
  - Opioid naïve
    - Morphine 1 mg PO/SL/buccal q4h and a 0.5 mg q1h PRN dose
    - Can consider using 5 mg q4h and a 2.5 mg PRN dosage if moderate dyspnea
    - Hydromorphone 0.25 – 1 mg PO/SL/buccal q4h with a 0.5 mg PRN dosage
  - Titrate to response
  - Can consider long acting if stable
- Patients who are already on an opioid for pain, can consider breakthrough opioid for pain OR dyspnea

Expert Rev Respir Med. 2013 Apr;7(2):123-34

Pharmacological Management

- Chemotherapy/Radiotherapy – Disease control
- Anxiolytics – Anxiety component
- Bronchodilator – If there is COPD or obstruction
- Diuretics – In congestive heart failure or pulmonary congestion
- Corticosteroid – Inflammation/obstruction
- Antibiotics - Infection
- Palliative sedation – If symptoms are refractory to other treatments

Non Pharmacological Management

- Facial cooling
  - Fanning over nose and mouth can improve breathlessness due to stimulation of mechanoreceptors in the face innervated by sensory nerves in the trigeminal nerve
- High Fowler's position
- Bed rest
- Good oral hygiene

Asia Pac J Oncol Nurs. 2017 Apr-Jun; 4(2): 162–167

Case Presentation

- B.B continues on her regular medications
- She has found that hydromorphone has been somewhat effective in managing dyspnea and has tried other non pharmacological options such as facial fanning
- Today she asks “My energy levels are not doing well. I have not been on treatment and I feel like I am tired all the time. Is there something that can help?
- She still spends more than 50% of her day out of bed and continues to sleep well at night
- Finding she needs more rest breaks in the day

Cancer Related Fatigue

Cancer Related Fatigue

- Subjective persistent tiredness or exhaustion
- Distressing for patient and caregivers
- Physical, emotional and cognitive strain resulting in decreased quality of life
- Treatment related?
  - May take years after chemotherapy treatment to improve
  - Delays or dose reductions in chemotherapy if on treatment
- Reduced baseline of energy
- Pharmacological management is rarely used in practice

Nat Rev Clin Oncol. 2014 Oct; 11(10): 597–609

Causes

- Pathophysiological changes
  - Increased inflammatory state
  - Hypothalamic-pituitary-adrenal (HPA) axis dysregulation
  - Autonomic nervous system dysregulation
- Treatment related
  - Chemotherapy
  - Radiotherapy
  - Hormonal treatment
- Other contributing factors
  - Comorbid conditions (i.e depression)
  - Sleep disturbances
  - Deconditioning/muscle loss
  - Poor coping/catastrophizing

Nat Rev Clin Oncol. 2014 Oct; 11(10): 597–609

Pharmacological Management

- Stimulants
  - Methylphenidate 5 mg titrated upwards to 20 mg
  - Review of 5 articles demonstrated a benefit over placebo
    - Only one trial was statistically significant
  - Fast onset, short term use
    - Should have effects within 48 hours
    - No evidence beyond 8 weeks
  - Consider adverse effects and interactions
    - Cardiovascular, anxiety, seizure risk
    - Serotonin syndrome with concomitant serotonin modulators?

J Pain Symptom Manage. 2011 Apr;41(4):761-7
Nat Rev Clin Oncol. 2014 Oct; 11(10): 597–609

Pharmacological Management

- Corticosteroids
  - Dexamethasone
    - Dexamethasone 4 mg PO BID for 14 days
    - Often used if there is another indication (i.e. pain control, appetite stimulation, improvement of status)
    - Improvement in quality of life and ESAS-physical distress scores at day 15
    - No difference statistical difference in adverse effects
    - Considered at end stages of life
    - Lowest effective dose
  - Megestrol and medroxyprogesterone no improvement

J Clin Oncol. 2013 Sep 1;31(25):3076-82
J Natl Cancer Inst. 2008 Aug 20;100(16):1155-66
Nat Rev Clin Oncol. 2014 Oct; 11(10): 597–609

Pharmacological Management

- Antidepressants
  - Paroxetine and sertraline no improvement
  - Consider if patient has depressive component
- Hematopoietic growth factor
  - Only significant if there is a component or chemotherapy induced anemia
- Anti cytokine agents
  - Some positive studies, but consider adverse effect and cost

J Natl Cancer Inst. 2008 Aug 20;100(16):1155-66
Lancet Oncol. 2007 Jul;8(7):603-12
Nat Rev Clin Oncol. 2014 Oct; 11(10): 597–609

Non Pharmacological Management

- Energy conservation
  - Identify what is important to patient and focus on those activities while cutting energy expenditure from other activities
- Exercise
- Short naps
  - Allow patients to rest when fatigued but preferably naps < 30 minutes
  - Sleep hygiene to prevent poor overnight sleep
  - Psychosocial intervention
  - Mind-body interventions
    - Meditation, yoga, acupuncture

Nat Rev Clin Oncol. 2014 Oct; 11(10): 597–609

Question Time

Which of the following is true about management of cancer related fatigue?

A. Methylphenidate can be used long term and should be trialed for at least 1 week
B. Megestrol is useful for improvement of quality of life
C. Dexamethasone can be trialed and if effective, consider the lowest effective dose in patients at the end of life
D. Avoid exercise and naps
E. None of the above

Answer

Which of the following is true about management of cancer related fatigue?

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Case Presentation

- B.B's husband returns to the pharmacy with questions regarding B.B's weight and status
- He has noticed that she continues to lose weight and is concerned with regards to how little she has been eating
- "She looks like skin and bones. Is there something I can do to help? Are there nutritional supplements that will help?"

Anorexia-Cachexia

Anorexia-Cachexia

- Anorexia – Loss of appetite
- Cachexia – Loss of skeletal muscle mass that is cannot be reversed by nutritional support
- Weight loss after excluding intentional causes
  - Weight loss comparing to pre-diagnosis weight
- Difficult to manage and distressing symptom for family members and patient
  - “I have to eat to maintain my strength”

Nat Rev Dis Primers. 2018 Jan 18;4:17105

Causes

- Complex pathophysiology not yet fully understood
  - Elevated resting energy expenditure
  - Increased inflammation and cytokine release
  - CNS changes
  - Depletion of adipose tissues and reduction of fat mass through lipolysis
  - Cardiac muscle atrophy

Nat Rev Dis Primers. 2018 Jan 18;4:17105

Corticosteroids

Dexamethasone

- Dose: 3 – 8 mg/day
- Improved appetite but no improvement in weight gain
- Short term improvement (2 weeks improvement vs. 4 weeks no improvement)
- Improvement in overall performance status, nausea control?

Methylprednisolone and prednisolone have shown improvement in overall well-being and appetite, but no weight gain

Nat Rev Dis Primers. 2018 Jan 18;4:17105
J Clin Oncol. 2005 Nov 20;23(33):8500-11

Progestins

Megestrol

- Dose: 480 to 800 mg/day
- Improvement in weight gain and appetite stimulation
- Superior compared to dronabinol for appetite stimulation

Medroxyprogesterone

- Dose: 300 – 1200 mg/day
- Improvement in appetite but not weight gain

Nat Rev Dis Primers. 2018 Jan 18;4:17105
J Clin Oncol. 2005 Nov 20;23(33):8500-11

Cannabinoids

Dronabinol

- Dose: 2.5 mg – 20 mg/day
- No improvement compared to placebo in caloric intake
- Inferior to megestrol
- Higher discontinuation rates vs. placebo due to adverse effects

Nabilone

- Dose: 0.5 mg – 1 mg/day
- Increased caloric intake
- Quality of life improvement

Nat Rev Dis Primers. 2018 Jan 18;4:17105
J Clin Oncol. 2005 Nov 20;23(33):8500-11
J Cachexia Sarcopenia Muscle. 2018 Apr; 9(2): 220–234
Support Care Cancer. 2018 Sep;26(9):3029-3038.

Antidepressant

Mirtazapine

- Dose: 15 – 30 mg/day
- Phase II trial with improvement in weight gain in non-depressed patients
- Clinical trials ongoing
- May stimulate appetite stimulation
  - Consideration in patients with depression and possibly non-depressed patients

Am J Hosp Palliat Care. 2010 Mar;27(2):106-10

Pharmacological Management

- Corticosteroids may be helpful for a short term response for increasing appetite
- Corticosteroids do not show an improvement in weight gain or cachexia. Consider long term adverse effects such as proximal myopathy and skeletal muscle atrophy
- Progestins may increase appetite but weight gain may be associated with fat mass and resulting muscle atrophy
- Progestins may increase thromboembolic events
- Cannabinoids increase caloric intake but no improvement in weight or cachexia
- Future of new cannabis products?

Non Pharmacological Management

- Dietician consultation
- Increase calories
  - High fat milks and creams
  - Lactose free milk
  - High fat cheese
  - Ice cream and yogurt inside smoothies, milkshakes or on top of fruits
  - Meal replacement drinks
  - Use meal replacement drinks in your milkshakes
  - Snack throughout the day
  - Eat every 2 – 3 hours
  - Try not to drink during meals but after meals
  - Eat calorie dense foods
  - Prepare meals in advanced

Question Time

Which of the following is true with regards to cancer related anorexia and cachexia management?

A. Dexamethasone may help improve appetite and weight gain
B. Progestins may help improve appetite and muscle growth
C. Cannabinoids increase caloric intake and weight gain
D. All of the above
E. None of the above

Answer

Which of the following is true with regards to cancer related anorexia and cachexia management?

A. Dexamethasone may help improve appetite and weight gain
B. Progestins may help improve appetite and muscle growth
C. Cannabinoids increase caloric intake and weight gain
D. All of the above
E. None of the above

Case Presentation

- You hear from B.B's husband who now says that B.B continues to deteriorate
- She now has been hospitalized due to confusion and agitation
- Her husband notes that she will not be coming home and will be going to hospice

Delirium

Delirium

- Occurs in up to 85% of advanced cancer patients in the last weeks of life
  - 1/3 of cases are missed and 1/2 of causes are reversible
- Management can be difficult and should be assessed case-by-case by palliative specialists
  - Pharmacist medication review
- Subtypes
  - Hyperactive – confusion, agitation, hallucinations, delusional, combative
  - Hypoactive – confusion, somnolence, withdrawn, lethargic sedated
  - Mixed
- Quick onset and transient

Nat Rev Neurol. 2009 Apr; 5(4): 210–220

Causes

- Not well understood
- Multiple causes in each case
- Treat the potential underlying causes
  - Drugs
  - Infection
  - Metabolic
  - Structural
  - Retention

BCMJ. 2011 Oct;53(8): 409-415

Causes

DIMS-R (Drugs, Infection, Metabolic, Structural, Retention): Common precipitating factors for delirium

Drugs
- Prescribed (narcotics, steroids, anticholinergic, NSAIDs)
- Over-the-counter (dimenhydrinate, diphenhydramine)
- Drug intoxication or withdrawal (alcohol, sedative-hypnotics, narcotics

Infection (urinary tract, lungs, skin, blood)

Metabolic disturbances
- Fluid (dehydration, hypovolemia)
- Electrolyte (sodium, potassium, magnesium)
- Nutrition (malnutrition, thiamine deficiency, anemia)

Structural insults
- Cardiovascular (angina, infarction, congestive heart failure)
- Central nervous system (stroke or ischemia, concussion)
- Pulmonary (hypoxia [e.g., COPD exacerbation])
- Gastrointestinal (bleeding with anemia, *C. difficile,* colitis)

Retention problems (urinary retention, constipation)

BCMJ. 2011 Oct;53(8): 409-415

Pharmacological Management

- Evidence is weak in this area
- Haloperidol
  - 1 mg PO/SC q8-12h and q1h PRN
  - Can be titrated to effect
  - Often first choice in helping with agitation and hallucinations
  - Anticholinergic, sedation, QTc prolongation, extrapyramidal symptoms, lowered seizure threshold
- Benzodiazepines are recommended by NCCN guidelines but lorazepam has shown minimal effects in some trials

Pharmacological Management

- Combination haloperidol and lorazepam
  - Haloperidol 2 mg and lorazepam 3 mg IV
  - Significant reduction in agitated delirium patients
  - Patient perceived to be more comfortable by nurses and family members
  - Consider the sedative effects and whether this is for the comfort of the patient, family, and/or caregivers
- Methotrimeprazine
  - 6.25 – 12.5 mg SC q8-12h with a breakthrough q1h PRN
  - More anticholinergic activity and more sedating than haloperidol
  - Lowered seizure threshold

JAMA. 2017 Sep 19;318(11):1047-1056

Non Pharmacological Management

- Counseling for family members and caregivers
  - Confusion and agitation may result in expressions that “look like pain” resulting in increased opioid breakthrough usage, worsening delirium
  - Comfort management is the most important aspect
  - Try to limit stressors
  - Balance chemical restraints and agitation/combative behavior
  - Avoid physical restraints
- If refractory, may consider palliative sedation

Palliative Sedation

- Inducing and maintaining a deep sedation for comfort of refractory symptoms
  - Not inducing or hastening death
- Purpose is to relieve refractory symptoms where all other measures have failed
  - Agitation/delirium – most common
  - Dyspnea
  - Exsanguination – often managed with PRN medication
  - Controversial: uncontrolled pain or emotional distress

Palliative Sedation

- Require informed consensus from patient (if possible) and family
  - Will no longer be able to communicate with patient
- Patient must be near death and experiencing refractory symptoms
  - Timing is important as tachyphylaxis is possible
- Goals of care must reflect the equivalent of comfort care and must be established
- Clear communication and documentation
- This is NOT Medical Assistance in Dying

Palliative Sedation

- Principle of the double effect
  - Primary therapeutic intent is to relieve suffering while recognizing there are unavoidable consequences and adverse effects such as compromising a patient's ability to breathe
  - Law recognizes that the principle of double effect is to sedate the patient to reduce symptoms and not to hasten death

Palliative Sedation

- Palliative specialist should be consulted
- Midazolam
  - Dosing: Bolus 5 mg then a drip at 1 mg/hour and titrated every 15 – 20 minutes by 1 mg/hour until sedation achieved
  - Rapid onset (3-5 minutes)
  - IV/SC routes (SC often utilized)
  - Short half life for IV (~3 hours with a range of 1.8 – 6.8 hours)
  - Titrate dose based on response

Palliative Sedation

- Ensure all PO meds discontinued
- Foley catheter in place
- Continue analgesics through SC/IV routes
- Peaceful and quiet environment

“You matter because you are you, and you matter to the end of your life. We will do all we can not only to help you die peacefully, but also to live until you die.”

- Dame Cicely Saunders

Acknowledgements

I would like to thank Dr. Allison Chabassol for helping review the material presented today